

## Autosomal Recessive Severe Congenital Neutropenia (Kostmann Disease) via *HAX1* gene sequencing (Test #446)

**Brief Description of Clinical Features:** Severe Congenital Neutropenia (SCN; OMIM 202700) comprises a heterogeneous group of disorders of myelopoiesis with varying symptoms and patterns of inheritance. SCN is characterized by absolute neutrophil counts (ANC) consistently below 500/ $\mu$ l and severe systemic bacterial infections beginning in early infancy (see Boxer and Newburger *Pediatr Blood Cancer* 49:609-614, 2007). Patients typically have recurrent fevers and develop sinusitis, gingivitis and other soft tissue infections. SCN and cyclic neutropenia share the same symptoms, however with cyclic neutropenia ANCs rise and fall with a periodicity of ~ 21-days. A hallmark of SCN is bone marrow ‘maturation arrest’; neutrophils differentiate only to the promyelocyte/myelocyte stage (see Kostman *Acta Paediatr Scand* 64:362-368, 1975). About 95% of patients respond to treatment with recombinant granulocyte-colony stimulating factor (G-CSF) with an increase in ANC (Bellanne-Chantelot et al. *Blood* 103:4119-4125, 2004; Freedman et al. *Blood* 96:429-436, 2000), however treated patients are still at risk of sepsis (Donini et al. *Blood* 109:4716-4723, 2007). SCN is a premalignant condition; patients are at an elevated risk of developing myelodysplastic syndrome and acute myeloblastic leukemia (MDS/AML). The risk of developing a malignancy increases upon G-CSF treatment (Gilman et al. *Blood* 36:576-585, 1970; Freedman et al. *Blood* 96:429-436, 2000; Rosenberg et al. *Blood* 107:4628-4635, 2006). In contrast to patients with SCN, MDS/AML have not been diagnosed in patients with cyclic or idiopathic neutropenia.

**Genetics:** Autosomal recessive forms of SCN have been linked to mutations in the *G6PC3* and *HAX1* genes. Patients with Kostmann Disease (Kostmann R. *Acta Paediatr* 45:1-78, 1956), autosomal recessive SCN due to mutations in the *HAX1* gene (OMIM 605998), may have neurological symptoms including cognitive dysfunction and epilepsy (Klein et al. *Nat Genet* 39:86-92, 2007; Germeshausen et al. *Blood* 111:4954-4957, 2008). *HAX1* encodes a ubiquitously expressed mitochondrial protein that has an anti-apoptotic function (Cilenti et al. *J Biol Chem* 279:50295-50301, 2004). Klein et al. (2007) showed that *HAX1* protects myeloid cells from apoptosis through its role in maintaining mitochondrial membrane potential. Consequently, disruption of normal *HAX1* function affects neutrophil development resulting in SCN.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 7 coding exons of the *HAX1* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100, \$190) or two exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

**Reference Sequences:** Genomic: **NC\_000001.10** mRNA: **NM\_006118.3** Protein: **NP\_006109.2 (CCDS 1064.1)**

**Indications for Test:** Patients with recurring bacterial infections, a family history of SCN, or neutropenia unrelated to other syndromes (e.g. Chediak-Higashi Syndrome, Hermansky Pudlak Syndrome, or Griscelli Syndrome).

**Sensitivity of Test:** Autosomal recessive forms of SCN account for ~ 40% of SCN cases.

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 2 – 3 weeks.

**Specimen Requirements:** See bottom of page 4 of Requisition Form

**Price:            Sequencing of *HAX1*            \$ 520**

CPT Codes							
Test	83890 x1	83891 x1	83898 x5	83904 x5	83894 x1	83912 x1	Total
<i>HAX1</i>	\$30	\$40	\$130	\$200	\$30	\$90	\$520

**Accreditation:** CLIA ID #52D1027685 (expires 1/18/13)    CAP #7185561, AU ID:1407125 (expires 12/20/12)

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